CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074932

Trade Name : ETODOLAC CAPSULES

Generic Name: Etodolac Capsules 200mg and 300mg

Sponsor : Mylan Pharmaceuticals, Inc.

Approval Date: May 16, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074932

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074932

APPROVAL LETTER

ANDA 74-932

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application dated July 31, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Etodolac Capsules, 200 mg and 300 mg.

Reference is also made to your amendments dated October 17, 1996, February 19, February 26, March 3, March 6 and March 13 and April 16, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Etodolac Capsules, 200 mg and 300 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug [Lodine® Capsules, 200 mg and 300 mg of Wyeth Ayerst Laboratories, Inc.]. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

5/16/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074932

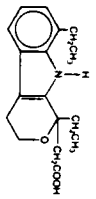
FINAL PRINTED LABELING

ETOD:R1

ETODOLAC CAPSULES

200 mg and 300 mg

DESCRIPTION: Etodolac is a pyranocarboxylic acid, chemically designated as (±) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. The structural formula for etodolac is shown below:



The molecular formula for etodolac is $C_{17}H_{21}NO_3$. The molecular weight of the base is 287.37. It has a pKa of 4.65 and an n-octanol-water partition coefficient of 11.4 at pH 7.4. Etodolac is a white crystalline compound, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol.

The inactive ingredients present in the capsules are ammonium hydroxide, black iron oxide, colloidal silicon dioxide, gelatin, magnesium stearate, microcrystalline cellulose, pharmaceutical glaze, polysorbate 80, povidone, red iron oxide, silicon dioxide, simethicone, sodium lauryl sulfate, sodium starch glycolate, titanium dioxide, and yellow iron oxide.

Etodolac is available in 200 and 300 mg capsules for oral administration.

CLINICAL PHARMACOLOGY: Pharmacology: Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechaanism of action of etodolac, like that of other NSAIDs, is not known but is believed to be associated with the inhibition of prostaglandin biosynthesis.

Etodolac is a racemic mixture of (-)R- and (+)S-etodolac. As with other NSAIDs, it has been demonstrated in animals that the (+)S-form is biologically active. Both enantiomers are stable and there is no (-)R to (+)S conversion *in vivo*.

Pharmacodynamics: Analgesia was demonstrable by 1/2 hour following single doses of 200 to 400 mg etodolac, with the peak effect occurring in 1 to 2 hours. The analgesic effect generally lasted for 4 to 6 hours (see Clinical Trials).

Pharmacokinetics: The pharmacokinetics of etodolac have been evaluated in 267 normal subjects, 44 elderly patients (> 65 years old), 19 patients with renal failure (creatinine clearance 37 to 88 mL/min), 9 patients on hemodialysis, and 10 patients with compensated hepatic cirrhosis.

Etodolac, when administered orally, exhibits kinetics that are well described by a two-compartment model with first-order absorption.

Etodolac has no apparent pharmacokinetic interaction when administered with phenytoin, glyburide, furosemide or hydrochlorothiazide.

Absorption: Etodolac is well absorbed and had a relative bioavailability of 100% when 200 mg capsules were compared with a solution of etodolac. Based on mass balance studies, the systemic availability of etodolac from the capsule formulation is at least 80% ... Excretio...

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Absorption: Etodolac is well absorbed and had a relative bioavailability of 100% when 200 mg capsules were compared with a solution of etodolac. Based on mass balance studies, the systemic availability of etodolac from the capsule formulation is at least 80%. Etodolac does not undergo significant first-pass metabolism following oral administration. Mean (± 1 SD) peak plasma concentrations range from approximately 14 ± 4 to 37 ± 9 mcg/mL after 200 to 600 mg single doses and are reached in 80 ± 30 minutes (see Table 1 for summary of pharmacokinetic parameters). The dose-proportionality based on AUC (the area under the plasma concentration-time curve) is linear following doses up to 600 mg every 12 hours. Peak concentrations are dose-proportional for both total and free etodolac following doses up to 400 mg every 12 hours, but following a 600 mg dose, the peak is about 20% higher than predicted on the basis of lower doses.

Table 1 of Etodolac Steady-State Pharmacokinetic Parameters (N=267)

Kinetic Parameters	Mean ± SD
Extent of oral absorption (bioavailability)(f)	≥ 80%
Oral-dose clearance(CL/f)	47 ± 16 mL/h/kg
Steady-state volume(V_{ss}/f)	362 ± 129 mL/kg
Distribution half-life($t_{1/2}$, α)	0.71 ± 0.50h
Terminal half-life($t_{1/2}$, β)	7.3 ± 4.0h

Antacid Effects: The extent of absorption of etodolac is not affected when etodolac is administered with an antacid. Coadministration with an antacid decreases the peak concentration reached by about 15 to 20%, with no measurable effect on time-to-peak.

Food Effects: The extent of absorption of etodolac is not affected when etodolac is administered after a meal. Food intake, however, reduces the peak concentration reached by approximately one half and increases the time-to-peak concentration by 1.4 to 3.8 hours.

Distribution: Etodolac has an apparent steady-state volume of distribution about 0.362 L/kg. Within the therapeutic dose range, etodolac is more than 99% bound to plasma proteins. The free fraction is less than 1% and is independent of etodolac total concentration over the dose range studied.

Metabolism: Etodolac is extensively metabolized in the liver, with renal elimination of etodolac and its metabolites being the primary route of excretion. The intersubject variability of etodolac plasma levels, achieved after recommended doses, is substantial.

Protein Binding: Data from *in vitro* studies, using peak serum concentrations at reported therapeutic doses in humans, show that the etodolac free fraction is not significantly altered by acetaminophen, ibuprofen, indomethacin, naproxen, penicillin, chlorpropamide, glipizide, glyburide, phenytoin, and probenecid.

Elimination: The mean plasma clearance of etodolac is 47 (± 16) mL/h/kg, and terminal disposition half-life is 7.3 (± 4.0) hours. Approximately 72% of the administered dose is recovered in the urine as the following, indicated as % of the administered dose:

-etodolac, unchanged	1%
-etodolac glucuronide	13%
-hydroxylated metabolite (6-, 7-, and 8-OH)	5%
-hydroxylated metabolite glucuronides	20%
-unidentified metabolites	33%

Fecal excretion accounted for 16% of the dose.

Special Populations: *Elderly Patients:* In clinical studies, etodolac clearance was reduced by about 15% in older patients (> 65 years of age). In these studies, age was shown not to have any effect on etodolac half-life or protein binding, and there was no change in expected drug accumulation. No dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics. The elderly may need dosage adjustment, however, on the basis of body size (see PRECAUTIONS: Geriatric Population), as they may be more sensitive to antiprostaglandin effects than younger patients (see PRECAUTIONS: Geriatric Population).

Renal Impairment: Studies in patients with mild-to-moderate renal impairment (creatinine clearance 37 to 88 mL/min) showed no significant differences in the disposition of total and free etodolac. In patients undergoing hemodialysis, there was a 50% greater apparent clearance of total etodolac, due to a 50% greater unbound fraction. Free etodolac clear-

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Hepatic Impairment: In patients with compensated hepatic cirrhosis, the disposition of total and free etodolac is not altered. Although no dosage adjustment is generally required in this patient population, etodolac clearance is dependent on hepatic function and could be reduced in patients with severe hepatic failure.

Clinical Trials: ***Analgesia:*** Controlled clinical trials in analgesia were single-dose, randomized, double-blind, parallel studies in three pain models, including dental extractions. The analgesic effective dose for etodolac established in these acute pain models was 200 to 400 mg. The onset of analgesia occurred approximately 30 minutes after oral administration. Etodolac 200 mg provided efficacy comparable to that obtained with aspirin (650 mg). Etodolac 400 mg provided efficacy comparable to that obtained with acetaminophen with codeine (600 mg + 60 mg). The peak analgesic effect was between 1 to 2 hours. Duration of relief averaged 4 to 5 hours for 200 mg of etodolac and 5 to 6 hours for 400 mg of etodolac as measured by when approximately half of the patients required remedication.

Osteoarthritis: The use of etodolac in managing the signs and symptoms of osteoarthritis of the hip or knee was assessed in double-blind, randomized, controlled clinical trials in 341 patients. In patients with osteoarthritis of the knee, etodolac, in doses of 600 to 1000 mg/day, was better than placebo in two studies. The clinical trials in osteoarthritis used b.i.d. dosage regimens.

INDICATIONS AND USAGE: Etodolac is indicated for acute and long-term use in the management of signs and symptoms of osteoarthritis. Etodolac is also indicated for the management of pain.

CONTRAINDICATIONS: Etodolac is contraindicated in patients with known hypersensitivity to etodolac. Etodolac should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to etodolac have been reported in such patients (see WARNINGS: Anaphylactoid Reactions).

WARNINGS: Risk of Gastrointestinal (GI) Ulceration, Bleeding, and Perforation With Nonsteroidal Anti-Inflammatory Drug (NSAID) Therapy: Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Although minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs, even in the absence of previous GI-tract symptoms. In patients observed in clinical trials of such agents for several months' to 2 years' duration, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months and in about 2% to 4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

Anaphylactoid Reactions: Anaphylactoid reactions may occur in patients without prior exposure to etodolac. Etodolac should not be given to patients with the aspirin triad. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other nonsteroidal anti-inflammatory drugs. Fatal reactions have been reported in such patients (see CONTRAINDICATIONS and PRECAUTIONS: Pre-existing Asthma). Emergency help should be sought

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Advanced Renal Disease: In cases with advance kidney disease, as with other NSAIDs, treatment with etodolac should only be initiated with close monitoring of the patient's kidney function (see PRECAUTIONS: Renal Effects).

Pregnancy: In late pregnancy, as with other NSAIDs, etodolac should be avoided because it may cause premature closure of the ductus arteriosus (see PRECAUTIONS: Teratogenic Effects: Pregnancy Category C).

PRECAUTIONS: General Precautions:

Renal Effects: As with other NSAIDs, long-term administration of etodolac to rats has resulted in renal papillary necrosis and other renal medullary changes. Renal pelvic transitional epithelial hyperplasia, a spontaneous change occurring with variable frequency, was observed with increased frequency in treated male rats in a 2-year chronic study.

A second form of renal toxicity encountered with etodolac, as with other NSAIDs, is seen in patients with conditions in which renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, or liver dysfunction; those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.

Etodolac metabolites are eliminated primarily by the kidneys. The extent to which the inactive glucuronide metabolites may accumulate in patients with renal failure has not been studied. As with other drugs whose metabolites are excreted by the kidney, the possibility that adverse reactions (not listed in ADVERSE REACTIONS) may be attributable to these metabolites should be considered.

Hepatic Effects: Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including etodolac. These abnormalities may disappear, remain essentially unchanged, or progress with continued therapy. Meaningful elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with etodolac. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with etodolac. Rare cases of liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), etodolac should be discontinued.

Hematological Effects: Anemia is sometimes seen in patients receiving NSAIDs including etodolac. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including etodolac, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

Fluid Retention and Edema: Fluid retention and edema have been observed in some patients taking NSAIDs, including etodolac. Therefore, etodolac should be used with caution in patients with fluid retention, hypertension, or heart failure.

Pre-existing Asthma: About 10% of patients with asthma may have aspirin-sensitive asthma. The use of aspirin in

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All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

Fluid Retention and Edema: Fluid retention and edema have been observed in some patients taking NSAIDs, including etodolac. Therefore, etodolac should be used with caution in patients with fluid retention, hypertension, or heart failure.

Pre-existing Asthma: About 10% of patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthmas has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, etodolac should not be administered to patients with this form of aspirin sensitivity and should be used with caution in all patients with pre-existing asthma.

Information for Patients: Etodolac, like other drugs of its class, can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, ADVERSE REACTIONS) and likely benefits of nonsteroidal anti-inflammatory drug treatment.

Patients on etodolac should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

Because serious gastrointestinal tract ulcerations and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulcerations and bleeding and should inform them of the importance of this follow-up (see WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with Nonsteroidal Anti-Inflammatory Therapy).

Patients should also be instructed to seek medical emergency help in case of an occurrence of anaphylactoid reactions (see WARNINGS).

Laboratory Tests: Patients on long-term treatment with etodolac, as with other NSAIDs, should have their hemoglobin or hematocrit checked periodically for signs or symptoms of anemia. Appropriate measures should be taken in case such signs of anemia occur.

If clinical signs and symptoms consistent with liver disease develop or if systemic manifestations occur (e.g., eosinophilia, rash, etc.) and if abnormal liver tests are detected, persist or worsen, etodolac should be discontinued.

Drug Interactions: ***Antacids:*** The concomitant administration of antacids has no apparent effect on the extent of absorption of etodolac. However, antacids can decrease the peak concentration reached by 15 to 20% but have no detectable effect on the time-to-peak.

Aspirin: When etodolac is administered with aspirin, its protein binding is reduced, although the clearance of free etodolac is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of etodolac and aspirin is not generally recommended because of the potential of increased adverse effects.

Warfarin: Short-term pharmacokinetic studies have demonstrated that concomitant administration of warfarin and etodolac results in reduced protein binding of warfarin, but there was no change in the clearance of free warfarin. There was no significant difference in the pharmacodynamic effect of warfarin administered alone and warfarin administered with etodolac as measured by prothrombin time. Thus, concomitant therapy with warfarin and etodolac should not require dosage adjustment of either drug. However, there have been a few spontaneous reports of prolonged prothrombin times in etodolac-treated patients receiving concomitant warfarin therapy. Caution should be exercised because interactions have been seen with other NSAIDs.

Cyclosporine, Digoxin, Lithium, Methotrexate: Etodolac, like other NSAIDs, through effects on renal prostaglandins may cause changes in the elimination of these drugs leading to elevated serum levels of digoxin, lithium, and methotrexate and increased toxicity. Nephrotoxicity associated with cyclosporine may also be enhanced. Patients receiving these drugs who are given etodolac, or any other NSAID, and particularly those patients with altered renal function, should be observed for the development of the specific toxicities of these drugs.

Phenylbutazone: Phenylbutazone causes increase (by about 80%) in the free fraction of etodolac. Although *in vivo* studies have not been done to see if etodolac clearance is changed by coadministration of phenylbutazone, it is not recommended that they be coadministered.

Drug/Laboratory Test Interactions: The urine of patients who take etodolac can give a false-positive reaction for urinary bilirubin (urobilin) due to the presence of phenolic metabolites of etodolac. Diagnostic dip-stick methodology, used to detect ketone bodies in urine, has resulted in false-positive findings in some patients treated with etodolac. Generally, this phenomenon has not been associated with other clinically significant events. No dose-relationship has been observed.

Etodolac treatment is associated with a small decrease in serum uric acid levels. In clinical trials, mean decreases of 1 to 2 mg/dl were observed in arthritic patients receiving etodolac (600 mg to 1000 mg/day) after 4 weeks of therapy. These levels then remained stable for up to one year of therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No carcinogenic effect of etodolac was observed in mice or rats receiving oral doses of 15 mg/kg/day (45 to 89 mg/m^2, respectively) or less for periods of 2 years or 18 months, respectively. Etodolac was not mutagenic in *in vitro* tests performed with *S. typhimurium* and mouse lymphoma cells as well as in an *in vivo* mouse micronucleus test. However, data from the *in vitro* human peripheral lymphocyte test showed an increase in the number of gaps (3.0 to 5.3% unstained regions in the chromatid without dislocation) among the etodolac-treated cultures (50 to 200 mcg/mL) compared to negative controls (2.0%); no other difference was noted between the controls and drug-treated groups. Etodolac showed no impairment of fertility in male and female

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Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** In teratology studies, isolated occurrences of alterations in limb development were found and included polydactyly, oligodactyly, syndactyly, and unossified phalanges in rats and oligodactyly and synostosis of metatarsals in rabbits. These were observed at dose levels (2 to 14 mg/kg/day) close to human clinical doses. However, the frequency and the dosage group distribution of these findings in initial or repeated studies did not establish a clear drug or dose-response relationship.

There are no adequate or well-controlled studies in pregnant women. Etodolac should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because of the known effects of NSAIDs on parturition and on the human fetal cardiovascular system with respect to closure of the ductus arteriosus, use during late pregnancy should be avoided.

Labor and Delivery: In rat studies with etodolac, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of etodolac on labor and delivery in pregnant women are unknown.

Nursing Mothers: It is not known whether etodolac is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from etodolac, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Population: As with any NSAID, however, caution should be exercised in treating the elderly, and when individualizing their dosage, extra care should be taken when increasing the dose because the elderly seem to tolerate NSAID side effects less well than younger patients. In patients 65 years and older, no substantial differences in the side-effect profile of etodolac were seen compared with the general population (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

ADVERSE REACTIONS: Adverse-reaction information for etodolac was derived from 2,629 arthritic patients treated with etodolac in double-blind and open-label clinical trials of 4 to 320 weeks in duration and worldwide postmarketing surveillance studies.

In clinical trials, most adverse reactions were mild and transient. The discontinuation rate in controlled clinical trials, because of adverse events, was up to 10% for patients treated with etodolac.

New patient complaints (with an incidence greater than or equal to 1%) are listed below by body system. The incidences were determined from clinical trials involving 465 patients with osteoarthritis treated with 300 to 500 mg of etodolac b.i.d. (i.e., 600 to 1000 mg per day).

Incidence Greater Than or Equal to 1%—Probably Causally Related:

Body as a whole: Chills and fever.

Digestive system: Dyspepsia (10%), abdominal pain*, diarrhea*, flatulence*, nausea*, constipation, gastritis, melena, vomiting.

Nervous system: Asthenia/malaise*, dizziness*, depression, nervousness.

Skin and appendages: Pruritus, rash.

Special senses: Blurred vision, tinnitus.

Urogenital system: Dysuria, urinary frequency.

*Drug-related patient complaints occurring in 3 to 9% of patients treated with etodolac.

Drug-related patient complaints occurring in fewer than 3%, but more than 1%, are unmarked.

Incidence Less Than 1%—Probably Causally Related (Adverse reactions reported only in worldwide postmarketing experience, not seen in clinical trials, are considered rarer and are italicized.)

Body as a whole: *Allergic reaction, anaphylactoid reaction.*

Cardiovascular system: Hypertension, congestive heart failure, flushing, palpitations, syncope, *vasculitis (including necrotizing and allergic).*

Digestive system: Thirst, dry mouth, ulcerative stomatitis, anorexia, eructation, elevated liver enzymes, *cholestatic hepatitis,* hepatitis, *cholestatic jaundice, duodenitis, jaundice, hepatic failure, liver necrosis,* peptic ulcer with or without bleeding and/or perforation, *intestinal ulceration, pancreatitis.*

prolactone reaction.

Cardiovascular system: Hypertension, congestive heart failure, flushing, palpitations, syncope, *vasculitis (including necrotizing and allergic).*

Digestive system: Thirst, dry mouth, ulcerative stomatitis, anorexia, eructation, elevated liver enzymes, *cholestatic hepatitis,* hepatitis, *cholestatic jaundice, duodenitis, jaundice, hepatic failure, liver necrosis,* peptic ulcer with or without bleeding and/or perforation, *intestinal ulceration, pancreatitis.*

Hemic and lymphatic system: Ecchymosis, anemia, thrombocytopenia, bleeding time increased, *agranulocytosis, hemolytic anemia, leukopenia, neutropenia, pancytopenia.*

Metabolic and nutritional: Edema, serum creatinine increase, *hyperglycemia in previously controlled diabetic patients.*

Nervous system: Insomnia, somnolence.

Respiratory system: Asthma.

Skin and appendages: Angioedema, sweating, urticaria, vesiculobullous rash, *cutaneous vasculitis with purpura, Stevens-Johnson syndrome,* hyperpigmentation, *erythema multiforme*

Special senses: Photophobia, transient visual disturbances.

Urogenital system: *Elevated BUN, renal failure, renal insufficiency, renal papillary necrosis.*

Incidence Less Than 1%—Causal Relationship Unknown (Medical events occurring under circumstances where causal relationship to etodolac is uncertain. These reactions are listed as alerting information for physicians)

Body as a whole: Infection, headache.

Cardiovascular system: Arrhythmias, myocardial infarction, cerebrovascular accident.

Digestive system: Esophagitis with or without stricture or cardiospasm, colitis.

Metabolic and nutritional: Change in weight.

Nervous system: Paresthesia, confusion.

Respiratory system: Bronchitis, dyspnea, pharyngitis, rhinitis, sinusitis.

Skin and appendages: Alopecia, maculopapular rash, photosensitivity, skin peeling.

Special senses: Conjunctivitis, deafness, taste perversion.

Urogenital system: Cystitis, hematuria, leukorrhea, renal calculus, interstitial nephritis, uterine bleeding irregularities.

OVERDOSAGE: Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain which are generally reversible with supportive care. Gastrointestinal bleeding can occur and coma has occurred following massive ibuprofen or mefenamic-acid overdose. Hypertension, acute renal failure, and respiratory depression may occur but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Gut decontamination may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). This should be accomplished via emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) with an osmotic cathartic. Forced diuresis, alkalinization of the urine, hemodialysis, or hemoperfusion would probably not be useful due to etodolac's high protein binding.

DOSAGE AND ADMINISTRATION: As with other NSAIDs, the lowest dose and longest dosing interval should be sought for each patient. Therefore, after observing the response to initial therapy with etodolac, the dose and frequency should be adjusted to suit an individual patient's needs.

Dosage adjustment of etodolac is generally not required in patients with mild to moderate renal impairment. Etodolac should be used with caution in such patients, because, as with other NSAIDs, it may further decrease renal function in some patients with impaired renal function. (See PRECAUTIONS, General Precautions: *Renal Effects*.)

Analgesia: The recommended total daily dose of etodolac for acute pain is up to 1000 mg, given as 200 to 400 mg every 6 to 8 hours. In some patients, if the potential benefits outweigh the risks, the dose may be increased to 1200 mg/day in order to achieve a therapeutic benefit that might not have been achieved with 1000 mg/day. Doses of etodolac greater than 1000 mg/day have not been adequately evaluated in well-controlled clinical trials.

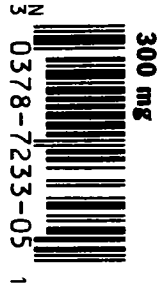
Osteoarthritis: The recommended starting dose of etodolac for the management of the signs and symptoms of osteoarthritis is 300 mg b.i.d., t.i.d., or 400 mg b.i.d., or 500 mg b.i.d. During long-term administration, the dose of etodolac may be adjusted up or down depending on the clinical response of the patient. A lower dose of 600 mg/day may suffice for long-term administration. In patients who tolerate 1000 mg/day, the dose may be increased to 1200 mg/day when a higher level of therapeutic activity is required. When treating patients with higher doses, the physician should observe sufficient increased clinical benefit to justify the higher dose. Physicians should be aware that doses above 1000 mg/day have not been ade-

MYLAN PHARMACEUTICALS INC

ETODOLAC CAPSULES
200 MG AND 300 MG

ANDA 74-932

Each capsule contains:
Etodolac ..... 300 mg



NDC 0378-7233-05

MYLAN®

ETODOLAC CAPSULES 300 mg

500 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

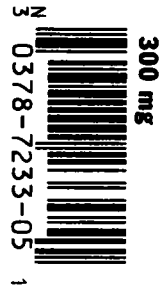
PROTECT FROM MOISTURE.

Usual Dosage: See accompanying information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM72338

Each capsule contains:
Etodolac ..... 300 mg



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Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM72338

MYLAN PHARMACEUTICALS INC

ETODOLAC CAPSULES
200 MG AND 300 MG

ANDA 74-932

N 3 0378-7233-01 3

300 mg

Each capsule contains:
Etodolac ...... 300 mg

NDC 0378-7233-01

MYLAN®

ETODOLAC CAPSULES 300 mg

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

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STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

PROTECT FROM MOISTURE.

Usual Dosage: See accompanying information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM7233A

N 3 0378-7233-01 3

300 mg

Each capsule contains:
Etodolac ...... 300 mg

NDC 0378-7233-01

MYLAN®

ETODOLAC CAPSULES 300 mg

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

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PROTECT FROM MOISTURE.

Usual Dosage: See accompanying information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM7233A

N 3 0378-7233-01 3

300 mg

Each capsule contains:
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NDC 0378-7233-01

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Usual Dosage: See accompanying information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM7233A

N 3 0378-7233-01 3

300 mg

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NDC 0378-7233-01

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PROTECT FROM MOISTURE.

Usual Dosage: See accompanying information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM7233A

MYLAN PHARMACEUTICALS INC

ETODOLAC CAPSULES
200 MG AND 300 MG

ANDA 74-932

N
3 0378-7200-01 5

200 mg

Each capsule contains:
Etodolac ...... 200 mg

NDC 0378-7200-01

MYLAN®

ETODOLAC CAPSULES 200 mg

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

PROTECT FROM MOISTURE.

Usual Dosage: See accompanying information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM7200A

N
3 0378-7200-01 5

200 mg

Each capsule contains:
Etodolac ...... 200 mg

NDC 0378-7200-01

MYLAN®

ETODOLAC CAPSULES 200 mg

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

PROTECT FROM MOISTURE.

Usual Dosage: See accompanying information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM7200A

N
3 0378-7200-01 5

200 mg

Each capsule contains:
Etodolac ...... 200 mg

NDC 0378-7200-01

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100 CAPSULES

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Usual Dosage: See accompanying information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM7200A

N
3 0378-7200-01 5

200 mg

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Etodolac ...... 200 mg

NDC 0378-7200-01

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Usual Dosage: See accompanying information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM7200A

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074932

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 74-932

3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals Inc
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION
Based on Lodine® (Wyeth-Ayerst). Patent 4,076,831 will expire on 2/28/97.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME
Etodolac Capsules

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
FDA: 1/24/97 NA letter faxed to firm.

Firm: 7/31/96 Orig. ANDA submitted.
10/17/96 Amendment(Bio)
2/19/97 Response to NA letter dated 1/24/97 (This review).
2/26/97 Tel.amendment
3/3/97 Amendment (labeling)
3/6/97 Tel.amendment
3/13/97 New corr.
4/16/97 New corr.

10. PHARMACOLOGICAL CATEGORY
Anti-inflammatory

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Capsules

14. POTENCY
200, 300 mg

16. RECORDS AND REPORTS N/A

18. CONCLUSIONS AND RECOMMENDATIONS
Approval

19. REVIEWER:
J.Fan

DATE COMPLETED:
2/27/97
5/6/97 (Revised)

cc: ANDA 74-932
DUP Jacket
Division File

Endorsements:

HFD-623/J.Fan 5/6/97
HFD-623/V.Sayeed, Ph.D. 5/6/97
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074932

BIOEQUIVALENCE REVIEW(S)

Dw

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-932 SPONSOR: Mylan pharmaceutical
DRUG: Etodolac
DOSAGE FORM: Capsules
STRENGTH(s): 200 mg and 300 mg
TYPE OF STUDY: Single/~~Multiple~~ Fasting/Fed
STUDY SITE:

STUDY SUMMARY: The firm's in vivo bioequivalence studies under fasting and nonfasting conditions are acceptable. The 90% CI for Ln AUC(0-t), Ln AUCinf and Cmax are within the acceptable range of 80-125% under fasting conditions. The ratios of the test mean to the reference mean are within the accepted range of 0.8-1.2 for the above parameters.

DISSOLUTION: Dissolution testing is acceptable. Waiver is granted for the 200 mg strength.

PRIMARY REVIEWER: BRANCH: III

INITIAL: DATE: 12/2/96

BRANCH CHIEF: BRANCH:

INITIAL: DATE: 12/4/96

Acting DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: DATE: 12/27/96

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: DATE:

9 w

ANDA 74-932

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. BOX 4310
Morgantown WV 26504-4310

JAN - 6 1997

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Etodolac Capsules 200 mg and 300 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following interim dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 1000 mL of phosphate buffer pH 7.5 (without enzyme) at 37°C using USP 23 apparatus 1 (Basket) at 100 rpm. The test product should meet the following specifications:

   Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DEC 27 1996 JV

Etodolac Capsules
200 and 300 mg
ANDA #74-932
Reviewer: Moheb H. Makary
WP 74932SDW.796

Mylan Pharmaceutical Inc.
Morgantown, WV
Submission date:
July 31, 1996
October 17, 1996

Review of Bioequivalence Studies, Dissolution Data and Waiver Request

I. Objective:

The firm has submitted two bioequivalence studies under fasting and nonfasting conditions on its 300 mg Etodolac Capsules and dissolution data to compare the test product relative to Lodine[R] 300 mg Capsules for review. The firm has also requested waiver of in vivo bioequivalence study requirements for its 200 mg strength. To support the request, the firm has submitted comparative dissolution profiles on its Etodolac 200 mg Capsules versus Lodine[R] 200 mg Capsules. The formulations for the drug products Etodolac 300 mg and 200 mg capsules were also submitted.

On October 17, 1995 Mylan submitted an amendment to its biostudies to clarify its decision to measure each of the R- and S-Etodolac enantiomers instead of measuring total Etodolac in the bioequivalence study biosamples. The firm also explained the basis of using a racemic mixture for preparation of the standard curves for R- and S-Etodolac.

II. Background

Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic activities. The drug is a racemic mixture of R- and S-etodolac, the S-form being biologically active. Both enantiomers are stable and there is no R-to-S conversion in-vivo. Etodolac is more than 99% bound to plasma proteins. The free fraction is less than 1% and is independent of etodolac total concentration. When administered orally, etodolac exhibits characteristics which are well described by a two-compartment model with first-order absorption. The systemic availability of etodolac is at least 80% and the drug does not undergo significant first-pass metabolism. Mean (±1 SD) peak plasma concentrations range from approximately 14 ±4 to 37 ±9 ug/ml after 200 to 600 mg single doses and are reached in 80 ±30 minutes. Terminal half-life is 7 ±4.0 hours. Intersubject variability of etodolac plasma levels, achieved after recommended doses, is substantial.

The extent of absorption of etodolac is not affected when

etodolac is administered after a meal or with an antacid. Food intake, however, reduces the peak concentration by approximately one half and increases the time to peak concentration by 1.4 to 3.8 hours.

The recommended dose of etodolac for acute pain is 200 to 400 mg every 6 to 8 hours, as needed, not to exceed a total daily dose of 1200 mg. Lodine[R] (Wyeth-Ayerst) is the innovator product and marketed strengths include 200 and 300 mg capsules and 400 mg tablets.

III. Protocol ETDL-9568 For Single Dose Fasting Bioequivalence Of Mylan's Etodolac 300 mg Capsules

Study site:

Analytical site: Mylan Pharmaceuticals Pharmacokinetics Laboratory
Morgantown, WV

Investigators:

Study date: Period I January 20-22, 1996
Period II February 3-5, 1996

Sample analysis: Sample analysis began on May 8, 1996 and was completed on May 30, 1996.

Study design: A single-dose, randomized, two-treatment, two-period, two-sequence crossover design.

Subjects: Thirty-nine (39) healthy male subjects entered the study. All thirty-nine subjects completed the study.

Selection criteria: Subjects selected for the study met the following acceptance criteria:

1. Ages 18 - 50 years, ± 10% of the ideal weight for his height as defined by Metropolitan Life Insurance Company Statistical Bulletin 1983.
2. Healthy, as determined by physical examination, medical history and clinical laboratory diagnostic tests (blood chemistry, hematology, urinalysis).

3. No concurrent illness, acute or chronic diseases or history of serious cardiovascular, pulmonary, endocrine, immunologic, dermatologic, renal, G.I., hepatic, hematologic, neurologic, or psychiatric disease.
4. No history of alcohol or drug abuse within the past year.
5. No history of hypersensitivity to etodolac or other nonsteroidal anti-inflammatory drugs.

Restrictions:

1. No ingestion of any alcohol, caffeine or xanthine-containing food or beverage within the 48 hours prior to initial dose of study medication.
2. Ingestion of any vitamins within the 48 hours prior to initial dose of study medication.
3. No Rx or OTC drugs beginning 14 days prior to the study.

Dose and treatment: All subjects completed an overnight fast (at least ten hours) before any of the following drug treatments:

Reference Product: a) 1x300 mg Lodine^{R} Capsule (Ayerst Laboratories), lot #3950568, Exp. 3/98, potency 98.9%, content uniformity 102.3(%CV=0.9).

Test Product: b) 1x300 mg Etodolac (Mylan), lot #2B006N, batch size capsules, Exp. N/A, potency 97.7% , content uniformity 98.4(%CV=0.7).

Washout period: Two weeks

Food and fluid intake: 1x300 mg Etodolac Capsule of either test or reference product was administered with 240 mL of water following a 10 hour fast. Subjects continued fasting for five hours post-dose. Water intake was not permitted from 2 hours before and until 2 hours after the dose.

Blood samples: Blood samples were collected at: 0 (prior to

dosing), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36 and 48 hours after dosing. Plasma was extracted and stored in labeled tubes at -20°C pending assay.

Assay Methodology

Statistical Methods

AUCL, AUCinf, Cpeak, Tpeak, Ke and T1/2 were calculated from the individual concentration versus time data for S- and R-etodolac. An analysis of variance (ANOVA) was applied to log-transformed and non-transformed bioequivalence parameters to determine any statistically significant ($p<0.05$) differences between the drug formulations. The 90% confidence intervals were calculated for

each bioequivalence parameter.

IV. In Vivo Results:

The study was conducted at
during the period of January 20 and February 5, 1996. Thirty-nine male subjects were enrolled and completed the study. All subjects tolerated the study well and no adverse experiences were reported.

The plasma concentrations for S-, R-etodolac and total etodolac are summarized in Table I, II and III. Total etodolac pharmacokinetic parameters were calculated from the summation of plasma concentrations of S-etodolac and R-etodolac.

Table I

Mean S-Etodolac Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 1x300 mg Etodolac Capsule Under Fasting Conditions
(N=39)

Time hr	Mylan Test Product Lot #2B006N ug/mL (CV%)	Ayerst Reference Product Lot #3950568 ug/mL (CV%)
0	0.00	0.00
0.25	0.60 (148)	0.49 (129)
0.50	2.55 (84.3)	2.43 (65.2)
0.75	2.86 (68.4)	2.54 (61.4)
1.00	2.26 (53.2)	2.27 (59.2)
1.25	1.86 (50.3)	2.12 (54.2)
1.50	1.67 (56.6)	1.97 (52.8)
1.75	1.53 (59.1)	1.76 (58.3)
2.00	1.26 (49.7)	1.68 (59.5)
2.50	0.97 (54.7)	1.06 (52.2)
3	0.98 (96.2)	0.80 (59.7)
4	0.47 (81.2)	0.39 (44.1)
5	0.27 (56.0)	0.24 (37.6)
6	0.15 (34.4)	0.14 (33.2)
8	0.06 (70.9)	0.06 (70.2)
10	0.03 (136)	0.02 (139)
12	0.01 (265)	0.001(624)
18	0	0
24	0	0
30	0	0

36	0	0
48	0	0

Pharmacokinetic Parameters

	Test	Reference	% Difference	90% CI log-transf
AUCL (ug.hr/mL)	6.1(23)	6.1(25)	0.0%	96-104
AUCinf (ug.hr/mL)	6.3(23)	6.3(25)	0.0%	96-104
Cpeak (ug/mL)	4.0(47)	4.0(30)	0.0%	83-105
Tpeak (hr)	1.33	1.22		
Kel(1/hr)	0.414	0.414		
t1/2 (hr)	2.1	1.9		

1. For Mylan's S-Etodolac, the mean AUCL, AUCinf and Cpeak values are the same as those for the reference product values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCL, AUCinf and Cpeak.

2. The S-Etodolac plasma levels peaked at 0.75 hour for both the test and reference products following their administration under fasting conditions.

Table II

Mean R-Etodolac Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 1x300 mg Etodolac Capsule Under Fasting Conditions
(N=39)

Time hr	Mylan Test Product Lot #2B006N ug/mL (CV%)	Ayerst Reference Product Lot #3950568 ug/mL (CV%)
0	0.00	0.00
0.25	1.14 (161)	0.98 (139)
0.50	7.96 (83.8)	7.86 (67.2)
0.75	12.10 (61.4)	11.70 (57.5)
1.00	12.80 (46.5)	12.60 (50.3)
1.25	12.50 (40.0)	13.30 (42.4)
1.50	12.50 (38.8)	13.70 (38.6)

1.75	12.10 (39.9)	13.80 (37.6)
2.00	11.60 (40.9)	13.60 (31.5)
2.50	10.80 (34.1)	12.20 (28.5)
3	10.80 (33.1)	11.10 (26.3)
4	8.80 (37.7)	8.61 (22.8)
5	7.57 (35.1)	7.21 (22.7)
6	5.09 (29.3)	5.01 (22.8)
8	3.08 (31.4)	3.10 (28.7)
10	2.54 (33.8)	2.47 (33.8)
12	1.99 (40.8)	1.90 (37.2)
18	0.20 (57.4)	0.93 (57.0)
24	0.61 (73.1)	0.60 (72.0)
30	0.26 (147)	0.28 (126)
36	0.12 (210)	0.09 (227)
48	0.02 (440)	0.01 (624)

Pharmacokinetic Parameters

	Test	Reference	% Difference	90% CI log-transf
AUCL (ug.hr/mL)	89.5(32)	90.0(29)	-0.6%	95-103
AUCinf (ug.hr/mL)	95.6(31)	96.5(30)	-0.9%	95-103
Cpeak (ug/mL)	18.1(27)	18.4(25)	-1.6%	92-104
Tpeak (hr)	1.74	1.56		
Kel(1/hr)	0.10	0.10		
t1/2 (hr)	8.32	8.83		

1. For Mylan's R-Etodolac, the mean AUCL, AUCinf and Cpeak values are 0.6%, 0.9% and 1.6% lower, respectively, than those for the reference product values. The differences are not statistically significant. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCL, AUCinf and Cpeak.

2. The R-Etodolac plasma levels peaked at 1 and 1.75 hours for the test and reference products, respectively, following their administration under fasting conditions.

Table III

Mean Total Etodolac Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 1x300 mg Etodolac Capsule Under Fasting Conditions

(N=39)

Time hr	Mylan Test Product Lot #2B006N ug/mL (CV%)	Ayerst Reference Product Lot #3950568 ug/mL (CV%)
0	0.00	0.00
0.25	1.74 (156)	1.47 (135)
0.50	10.50 (83.4)	10.30 (66.4)
0.75	14.90 (61.7)	14.20 (57.6)
1.00	15.00 (46.6)	14.80 (50.5)
1.25	14.40 (40.3)	15.40 (42.7)
1.50	14.20 (39.9)	15.70 (38.8)
1.75	13.70 (40.7)	15.50 (38.3)
2.00	12.90 (40.9)	15.30 (32.5)
2.50	11.80 (34.4)	13.30 (29.1)
3	11.80 (36.6)	11.90 (27.4)
4	9.27 (38.9)	9.00 (22.7)
5	7.85 (35.1)	7.49 (22.4)
6	5.24 (28.9)	5.15 (22.5)
8	3.14 (31.3)	3.16 (28.9)
10	2.57 (33.8)	2.49 (33.9)
12	2.00 (41.0)	1.90 (37.2)
18	0.10 (57.4)	0.93 (57.0)
24	0.61 (73.1)	0.60 (72.0)
30	0.26 (147)	0.28 (126)
36	0.12 (210)	0.09 (227)
48	0.02 (440)	0.01 (624)

Pharmacokinetic Parameters

	Test	Reference	% Difference	90% CI log-transf
AUCL (ug.hr/mL)	95.7(31)	96.2(28)	-0.5%	95-103
AUCinf (ug.hr/mL)	101.0(30)	103.0(29)	-1.9%	95-103
Cpeak (ug/mL)	21.7(30)	21.9(25)	-0.9%	91-104
Tpeak (hr)	1.71	1.42		

Kel(1/hr)	0.10	0.10
t1/2 (hr)	8.44	8.82

1. For Mylan Total-Etodolac, the mean AUCL, AUCinf and Cpeak values are 0.5%, 1.9% and 0.9% lower, respectively, than those for the reference product values. The differences are not statistically significant. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCL, AUCinf and Cpeak.

2. The Total-Etodolac plasma levels peaked at 1 and 1.5 hours for the test and reference products, respectively, following their administration under fasting conditions.

V. Study #ETDL-9591 For Single Dose post-prandial Bioequivalence Study

Objective: The objective of the study is to compare the relative bioavailability of Etodolac 300 mg Capsules (Mylan) with that of Lodine® 300 mg Capsules (Wyeth-Ayerst Laboratories) in healthy male volunteers under-nonfasting conditions, and to compare the difference in plasma levels after dosing with the test product when dosed with and without food.

Study site:

Analytical site: Mylan Pharmaceuticals Pharmacokinetics Laboratory
Morgantown, WV

Investigators:

Study date: Period I March 14-16, 1996
Period II March 21-23, 1996
Period III March 28-30, 1996

Sample analysis: Sample analysis began on May 28, 1996 and was completed on June 13, 1996.

Study design: A single-dose, randomized, three-treatment, three-period, six-sequence crossover design.

Subjects: Nineteen (19) healthy male subjects entered and completed the study.

Selection criteria: Same as Study #ETDL-9568 above.

Washout period: One week

Dose and treatment: Treatment A:
1x300 mg Lodine[R] Capsule (Wyeth-Ayerst Laboratories), lot #3950568, administered following a standard meal preceded by an overnight fast.
Treatment B:
1x300 mg Etodolac Capsule (Mylan), lot #2B006N administered following a standard meal preceded by an overnight fast.
Treatment C:
1x300 mg Etodolac Capsule (Mylan), lot #2B006N administered after an overnight fast.

Food and fluid intake: Subjects were required to fast overnight for 10 hours prior to dosing in each treatment phase. Subjects on regimen C ingested the capsule with 240 mL of water. Subjects on regimen A and B ingested the capsule with 240 mL of water within 30 minutes after a standardized high-fat breakfast (1 fried egg, 1 serving of hashed browned potatoes, 1 slice Canadian bacon, 1 buttered English muffin, 1 slice American cheese, 8 ounces of whole milk and 6 ounces of orange juice). Water was not permitted from 2 hours before and until 2 hours after the dose, but was allowed at all other times. Subjects received a standard meal 5 hours post-dose followed by an evening meal 10 hours after dosing and snacks at appropriate times thereafter.

Blood samples: Ten milliliters of venous blood were collected at: 0 (prior to dosing), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 18, 24, 30, 36 and 48 hours after dosing. The plasma was extracted and stored in labeled tubes at -20°C pending assay.

Assay Methodology Same as Study #ETDL-9568 above.

Statistical Methods Same as Study #ETDL-9568 above.

VI. In Vivo Results:

The study was conducted at during the period of March 14 to March 30, 1996. Nineteen healthy male subjects enrolled and completed

the study. There were two adverse events reported (subjects #16 and #19) as possibly drug related. These adverse events were as mild headaches. There were no serious or life threating events reported for this study. Both products appear to be equally well tolerated.

The plasma concentrations for S-, R-etodolac and total etodolac are summarized in Table IV, V and VI. Total etodolac pharmacokinetic parameters were calculated from the summed plasma concentrations of S-etodolac and R-etodolac.

Table IV

Mean S-Etodolac Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 1x300 mg Etodolac Capsule Under Fasting and Nonfasting Conditions
(N=19)

Time hr	A Ayerst Test Product Lot #3950568 Nonfasting ug/mL (CV%)	B Mylan Test Product Lot #2B006N Nonfasting ug/mL (CV%)	C Mylan Test Product Lot #2B006N Fasting ug/mL (CV%)
0	0.00	0.00	0.00
0.5	0.22 (136)	0.26 (204)	2.12 (79.7)
1	0.66 (136)	0.49 (106)	2.24 (64.4)
1.50	0.89 (64.5)	0.83 (73.1)	1.94 (79.6)
2	1.02 (42.7)	0.98 (55.6)	1.17 (62.9)
2.5	0.91 (42.2)	0.90 (51.3)	0.82 (62.0)
3	0.86 (49.3)	0.86 (51.7)	0.60 (59.3)
3.5	0.80 (41.9)	0.86 (52.7)	0.42 (52.8)
4	0.76 (46.0)	0.86 (79.8)	0.30 (45.0)
4.5	0.65 (55.0)	0.67 (54.1)	0.24 (47.8)
5	0.53 (54.3)	0.51 (69.2)	0.20 (46.6)
6	0.22 (43.5)	0.22 (50.4)	0.11 (47.0)
8	0.09 (61.9)	0.10 (77.4)	0.04 (129)
10	0.05 (85.3)	0.06 (116)	0.01 (302)
12	0.01 (300)	0.01 (240)	0.00
18	0.00	0.00	0.00
24	0.00	0.00	0.00
30	0.00	0.00	0.00
36	0.00	0.00	0.00
48	0.00	0.00	0.00

Pharmacokinetic Parameters for S-Etodolac

	A Reference Nonfasting	B Test Nonfasting	C Test Fasting	B/A
AUCL (ug.hr/mL)	4.3(29)	4.3(35)	5.3(38)	1.00
AUCinf (ug.hr/mL)	4.5(28)	4.5(35)	5.5(37)	1.01
Cpeak (ug/mL)	1.4(43)	1.5(46)	3.5(45)	1.03
Tpeak(hr)	2.42	2.34	0.92	
Kel(1/hr)	0.50	0.50	0.50	
t1/2 (hr)	1.67	1.9	1.6	

1. For Mylan's S-Etodolac, the mean AUCL, AUCinf and Cpeak values are 0.23%, 0.66% and 2.8% higher, respectively, than those for the reference product values under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUCL, AUCinf and Cpeak.

2. The S-Etodolac plasma levels peaked at 2 hours for both the test and reference products following their administration under nonfasting conditions.

Table V

Mean R-Etodolac Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 1x300 mg Etodolac Capsule Under Fasting and Nonfasting Conditions
(N=19)

Time hr	A Ayerst Test Product Lot #3950568 Nonfasting ug/mL (CV%)	B Mylan Test Product Lot #2B006N Nonfasting ug/mL (CV%)	C Mylan Test Product Lot #2B006N Fasting ug/mL (CV%)
0	0.00	0.00	0.00
0.5	0.71 (145)	0.72 (219)	7.05 (78.5)
1	2.63 (120)	2.19 (121)	12.90 (50.0)
1.50	4.59 (75.5)	4.30 (76.6)	13.50 (30.5)
2	6.54 (41.9)	6.07 (45.7)	11.90 (35.6)
2.5	7.40 (30.6)	7.10 (32.1)	10.40 (34.9)
3	7.88 (29.4)	7.56 (34.5)	9.38 (33.6)
3.5	8.23 (25.7)	8.14 (30.2)	8.40 (34.4)

4	8.59 (28.7)	8.88 (32.1)	7.44 (33.6)
4.5	8.80 (30.8)	8.86 (25.0)	6.78 (30.3)
5	8.51 (26.2)	8.35 (27.8)	6.48 (32.6)
6	6.07 (32.8)	5.77 (30.3)	4.34 (34.2)
8	3.42 (33.4)	3.42 (31.9)	2.75 (33.1)
10	2.66 (36.4)	2.60 (36.1)	2.26 (36.4)
12	1.98 (38.9)	2.02 (40.4)	1.68 (36.8)
18	1.03 (42.7)	0.96 (42.1)	0.85 (49.6)
24	0.57 (75.6)	0.54 (76.0)	0.49 (94.2)
30	0.22 (145)	0.26 (118)	0.21 (141)
36	0.04 (436)	0.03 (436)	0.04 (436)
48	0.00	0.00	0.00

Pharmacokinetic Parameters for R-Etodolac

	A Reference Nonfasting	B Test Nonfasting	C Test Fasting	B/A
AUCL (ug.hr/mL)	72.8(30)	71.1(27)	79.9(32)	0.98
AUCinf (ug.hr/mL)	78.3(30)	77.1(27)	86.4(32)	0.98
Cpeak (ug/mL)	10.2(23)	10.1(24)	16.3(23)	0.99
Tpeak(hr)	3.63	3.21	1.26	
Kel(1/hr)	0.10	0.10	0.10	
t1/2 (hr)	7.16	8.01	8.1	

1. For Mylan's R-Etodolac, the mean AUCL, AUCinf and Cpeak values are 2.3%, 1.53% and 1.0% lower, respectively, than those for the reference product values under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUCL, AUCinf and Cpeak.

2. The R-Etodolac plasma levels peaked at 4 and 4.5 hours for the test and reference products, respectively, following their administration under nonfasting conditions.

Table VI

Mean Total-Etodolac Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 1x300 mg Etodolac Capsule Under Fasting and Nonfasting Conditions
(N=19)

Time hr	A Ayerst Test Product Lot #3950568 Nonfasting ug/mL (CV%)	B Mylan Test Product Lot #2B006N Nonfasting ug/mL (CV%)	C Mylan Test Product Lot #2B006N Fasting ug/mL (CV%)
0	0.00	0.00	0.00
0.5	0.93 (142)	0.98 (214)	9.17 (78.2)
1	3.28 (122)	2.68 (118)	15.20 (49.9)
1.50	5.48 (73.0)	5.14 (74.6)	15.40 (33.5)
2	7.56 (40.9)	7.05 (45.2)	13.00 (37.2)
2.5	8.31 (30.7)	8.00 (32.2)	11.20 (35.9)
3	8.74 (30.3)	8.43 (35.7)	9.98 (34.5)
3.5	9.02 (26.4)	9.00 (30.7)	8.82 (34.6)
4	9.34 (29.5)	9.74 (35.0)	7.74 (33.4)
4.5	9.45 (31.8)	9.53 (26.1)	7.02 (30.3)
5	9.05 (26.4)	8.86 (29.4)	6.69 (32.5)
6	6.29 (32.3)	5.99 (30.6)	4.45 (34.1)
8	3.51 (33.3)	3.52 (32.6)	2.78 (33.6)
10	2.71 (36.4)	2.66 (36.9)	2.26 (36.2)
12	1.98 (39.1)	2.03 (40.9)	1.68 (36.8)
18	1.03 (42.7)	0.96 (42.1)	0.85 (49.6)
24	0.57 (75.6)	0.54 (76.0)	0.49 (94.2)
30	0.22 (145)	0.26 (118)	0.21 (141)
36	0.04 (436)	0.03 (436)	0.04 (436)
48	0.00	0.00	0.00

Pharmacokinetic Parameters for Total Etodolac

	A Reference Nonfasting	B Test Nonfasting	C Test Fasting	B/A
AUCL (ug.hr/mL)	77.2(29)	75.5(26)	85.2(31)	0.98
AUCinf (ug.hr/mL)	82.7(29)	81.5(26)	91.7(32)	0.99
Cpeak (ug/mL)	11.3(23)	11.4(26)	19.3(25)	1.00
Tpeak (hr)	3.50	3.05	1.24	

Kel(1/hr)	0.10	0.10	0.10
t1/2 (hr)	7.15	7.98	8.0

1. For Mylan Total-Etodolac, the mean AUCL, AUCinf and Cpeak values are 2.3%, 1.53% and 1.0% lower and higher, respectively, than those for the reference product values under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUCL, AUCinf and Cpeak.

2. The Etodolac plasma levels peaked at 4 and 4.5 hours for the test and reference products, respectively, following their administration under nonfasting conditions.

3. The mean Cpeak of the test product was reduced by 41%, when dosed under nonfasting conditions compared to fasting conditions. This reduction in Cpeak value is in agreement with the reference product's labeling which indicated that food intake, reduces the peak concentration reached by approximately one half, and increases the time-to-peak concentration by 1.4 to 3.8 hours.

VII. Formulations:

Mylan's comparative formulations for its Etodolac 200 mg and 300 mg capsules are shown in Table VII.

VIII. Dissolution:

Method:	USP 23 apparatus I (basket) at 100 rpm
Medium:	1000 mL of pH 7.5 phosphate buffer, 0.05 M
Number of Capsules:	12
Test products:	Mylan's Etodolac 200 mg Capsules, lot #2B005N 300 mg Capsules, lot #2B006N
Reference products:	Ayerst's Lodine 200 mg Capsules, lot #3950567 300 mg Capsules, lot #3950568
Specifications:	NLT in 20 minutes.

Dissolution testing results are shown in Table VIII.

IX. Comments :

1. The firm indicated that etodolac is presently commercially available only in the racemic form. The (S) enantiomer is biologically active but it accounts for 5-10% of the parent drug in plasma. For this reason, a stereospecific assay was employed in this assessment of bioequivalence, with quantitation of both the R and S isomers of etodolac. However, by the time the firm

was advised by the DBE to measure total etodolac, the biosamples had already been analyzed.

2. The firm's in vivo bioequivalence studies under fasting and nonfasting conditions are acceptable. The test product is similar in both rate and extent of absorption to the reference product. The 90% confidence intervals for LnAUCL, LnAUCinf and LnCpeak are within the acceptable range of 80-125% under fasting conditions for S-Etodolac, R-Etodolac and Total-Etodolac. The ratios of the test mean to the reference mean were within the acceptable range of 0.8-1.2 for AUCL, AUCinf and Cpeak under nonfasting conditions.

3. The in vitro dissolution testing submitted by the firm on its Etodolac 200 mg and 300 mg Capsules is acceptable.

4. The formulation for Etodolac 200 mg capsules is proportionally similar to the 300 mg strength of the test product.

X. Recommendations:

1. The bioequivalence studies conducted by Mylan Pharmaceuticals Inc., under fasting and nonfasting conditions on its Etodolac, 300 mg Capsule, lot #2B006N, comparing it to Wyeth-Ayerst Laboratories' Lodine^{R} 300 mg Capsule have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Mylan's Etodolac Capsule, 300 mg is bioequivalent to the reference product, Lodine^{R}, 300 mg Capsule, manufactured by Wyeth-Ayerst Laboratories.

2. The dissolution testing conducted by the firm on its Etodolac Capsules, 200 mg and 300 mg, lot #2B005N and #2B006N, respectively, is acceptable. The formulation for the 200 mg strength is proportionally similar to the 300 mg strength of the test product which underwent acceptable bioequivalence testing. Waiver of in vivo bioequivalence study requirements for the 200 mg capsule of the test product is granted. The Division of Bioequivalence deems Etodolac Capsules 200 mg, manufactured by Mylan Pharmaceuticals Inc., to be bioequivalent to Lodine^{R} Capsules 200 mg, manufactured by Wyeth-Ayerst Laboratories.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of phosphate buffer pH 7.5 (without enzyme) at 37^{o}C using USP 23 apparatus 1 (Basket) at 100 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of the drug in

the dosage form is dissolved in 20 minutes.

The firm should be informed of the above recommendations.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE Date: 12/4/96

Concur: Date: 12/27/96
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

MMakary/12-2-96 wp 74932SDW.796
cc: ANDA #74-932,original, HFD-658 (Makary), Drug File, Division File.

Table VIII. In Vitro Dissolution Testing

Drug (Generic Name): Etodolac Capsuless
Dose Strength: 200 mg and 300 mg
ANDA No.: 74-932
Firm: Mylan Pharmaceuticals Inc.
Submission Date: July 31, 1996
File Name: 74932SDW.796

I. Conditions for Dissolution Testing:

USP XXII Basket: X Paddle: RPM: 100
No. Units Tested: 12
Medium: 1000 mL of phosphate buffer pH 7.5
Specifications: NLT in 20 minutes
Reference Drug: Lodine
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

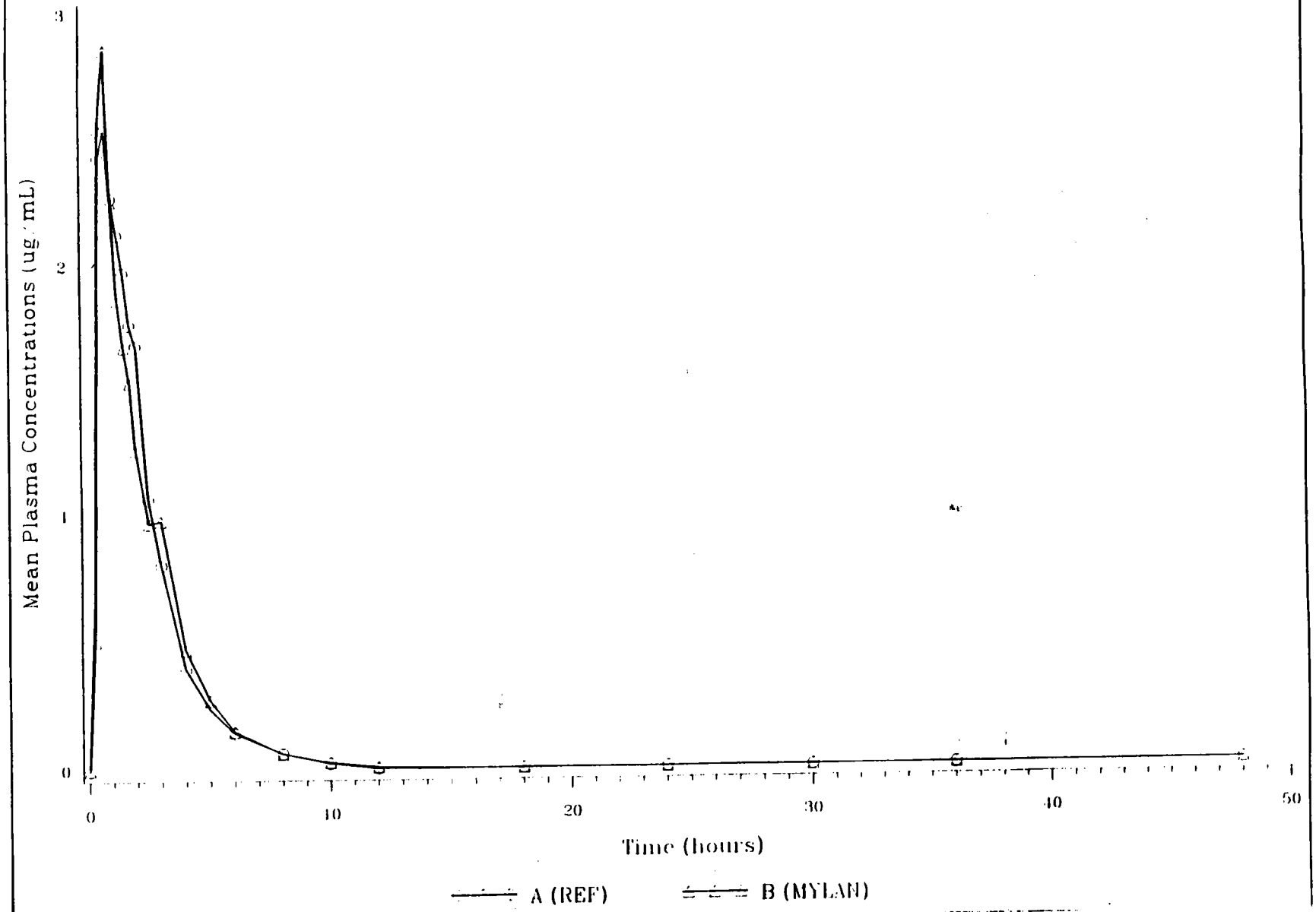
Sampling Times (Minutes)	Test Product Lot # 2B005N Strength(mg) 200			Reference Product Lot # 3950567 Strength(mg) 200		
	Mean %	Range	%CV	Mean %	Range	%CV
10	83		4.7	93		4.1
20	94		3.7	99		1.5
30	96		3.4	100		1.0

Sampling Times (Minutes)	Test Product Lot # 2B006N Strength(mg) 300			Reference Product Lot # 3950568 Strength(mg) 300		
	Mean %	Range	%CV	Mean %	Range	%CV
10	85		5.8	85		4.4
20	95		3.0	95		1.7
30	96		2.8	96		1.9

ETODOLAC (ETDL 39000)

Total Dose: 300 mg (1x300mg Capsule) Capsule, Study Type: Fasting

Mean s-etodolac Plasma Concentrations

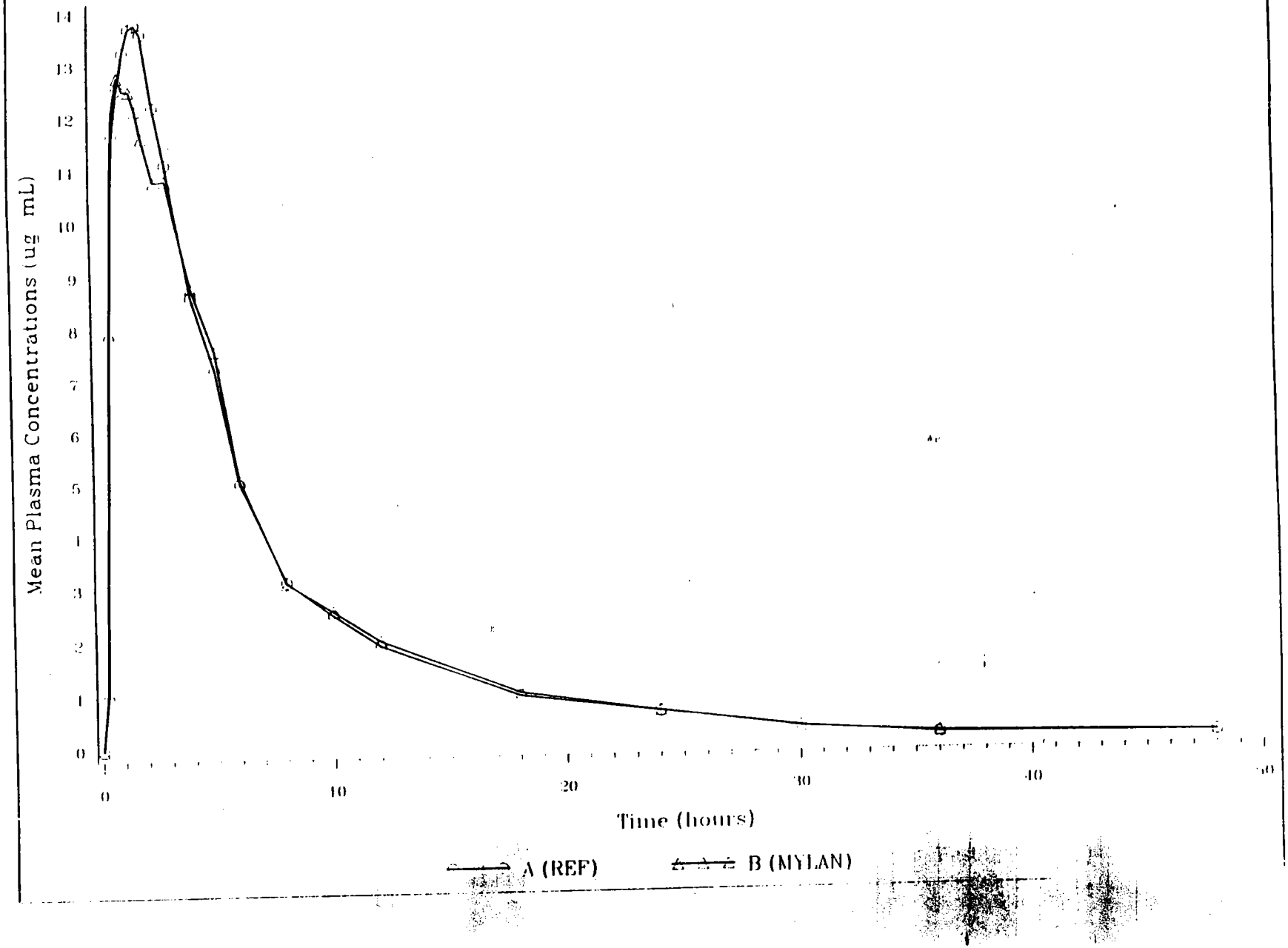


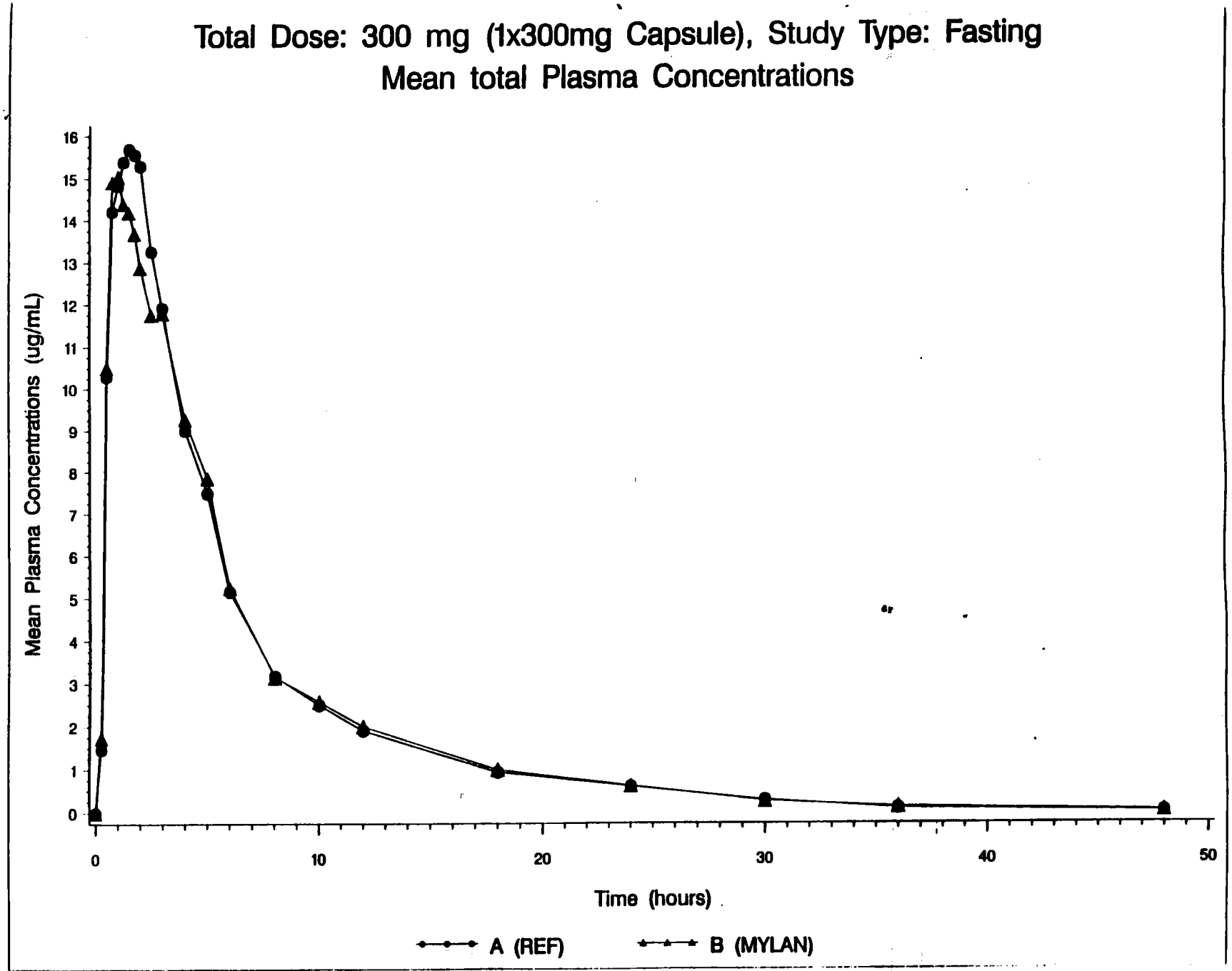
47 0

ETODOLAC (ETDL- 9568)

Total Dose: 300 mg (1x300mg Capsule) Capsule, Study Type: Fasting

Mean r-etodolac Plasma Concentrations

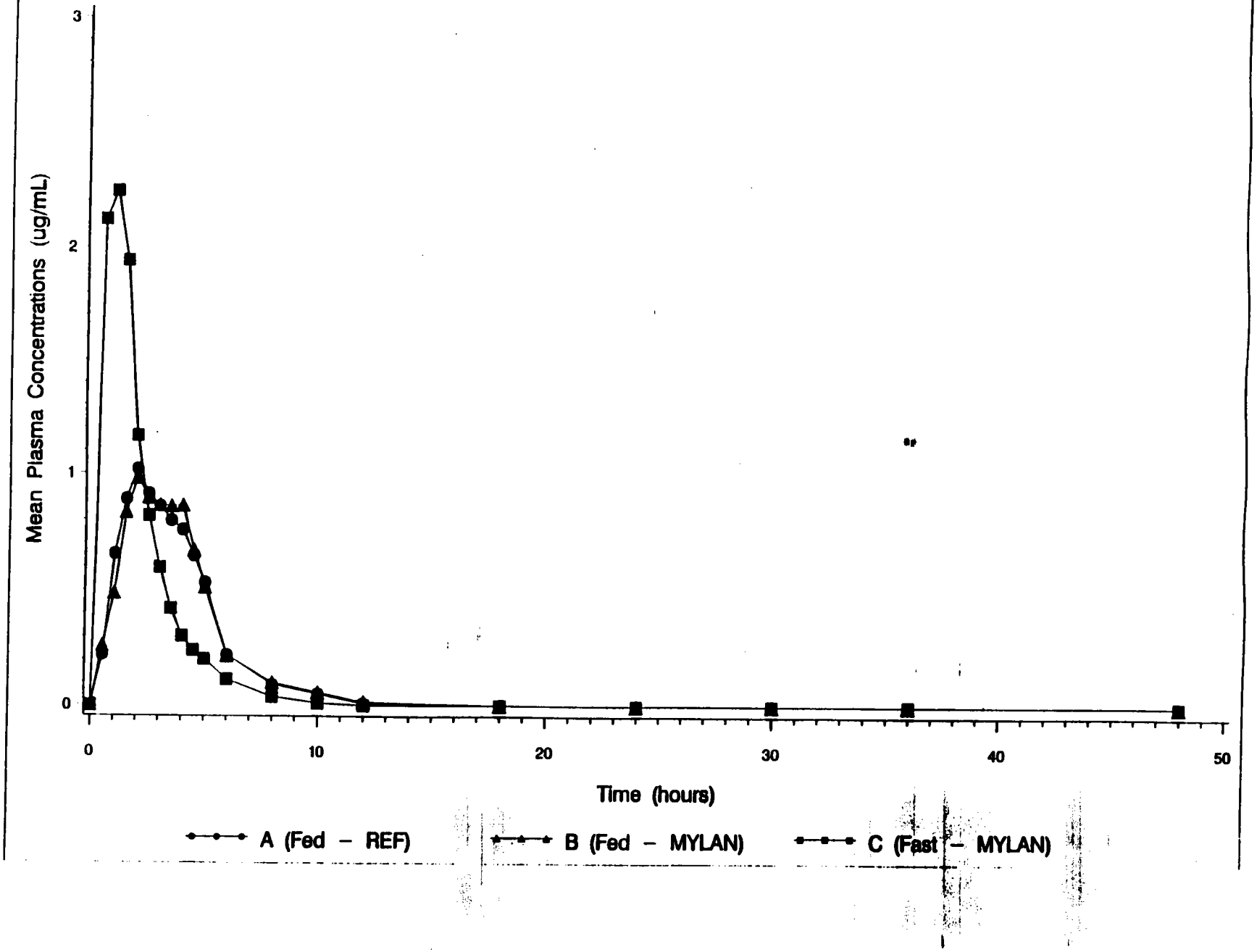



Total Dose: 300 mg (1x300mg Capsule), Study Type: Fasting
Mean total Plasma Concentrations
Mean Plasma Concentrations (ug/mL)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
0
10
20
30
40
50
Time (hours)
A (REF)
B (MYLAN)

ETODOLAC (ETDL – 9591)

Total Dose: 300 mg (1x300mg Capsule), Study Type: Fed

Mean s – etodolac Plasma Concentrations

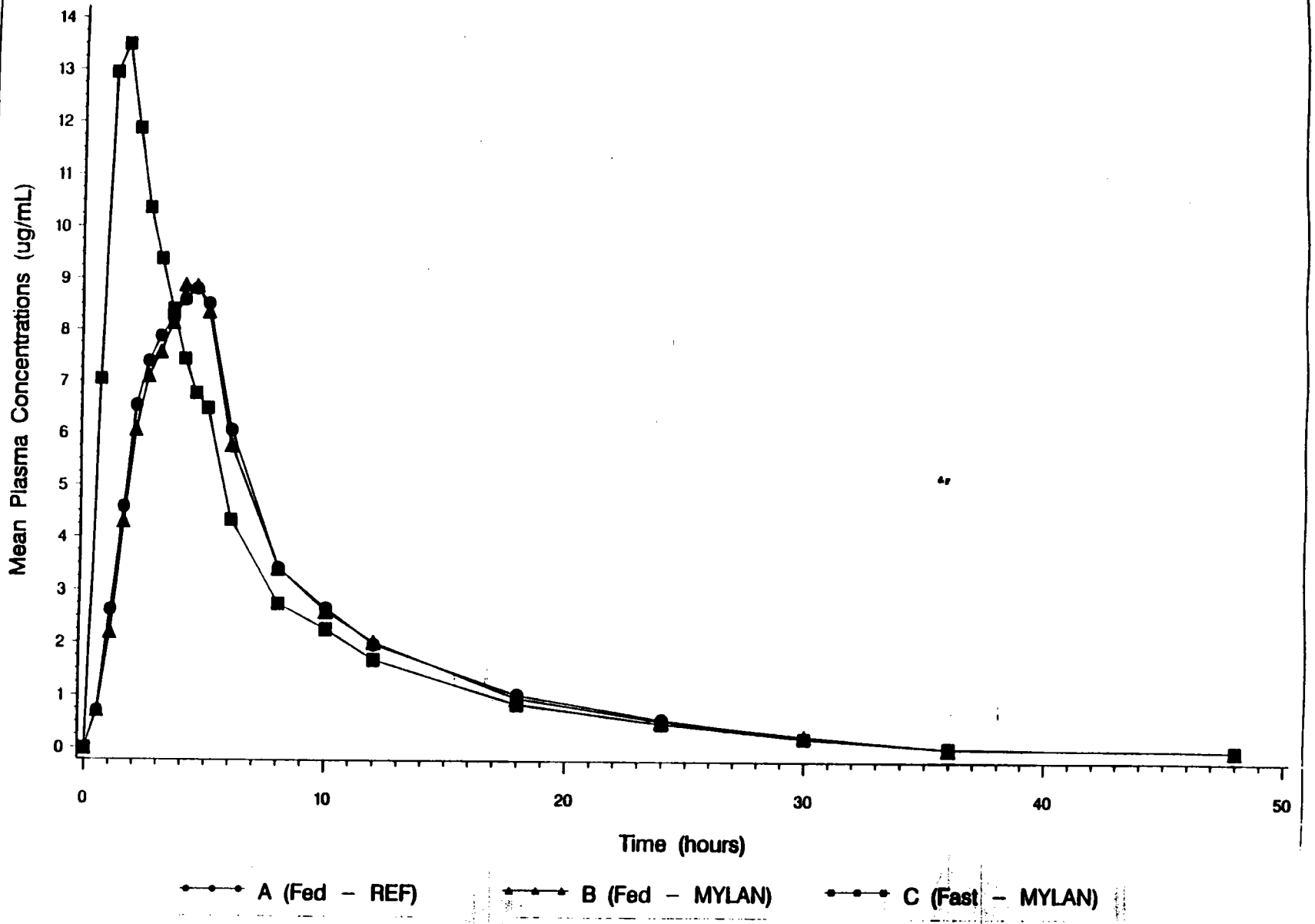


ATTACHMENT 1

ETODOLAC (ETDL-9591)

Total Dose: 300 mg (1x300mg Capsule), Study Type: Fed

Mean r-etodolac Plasma Concentrations



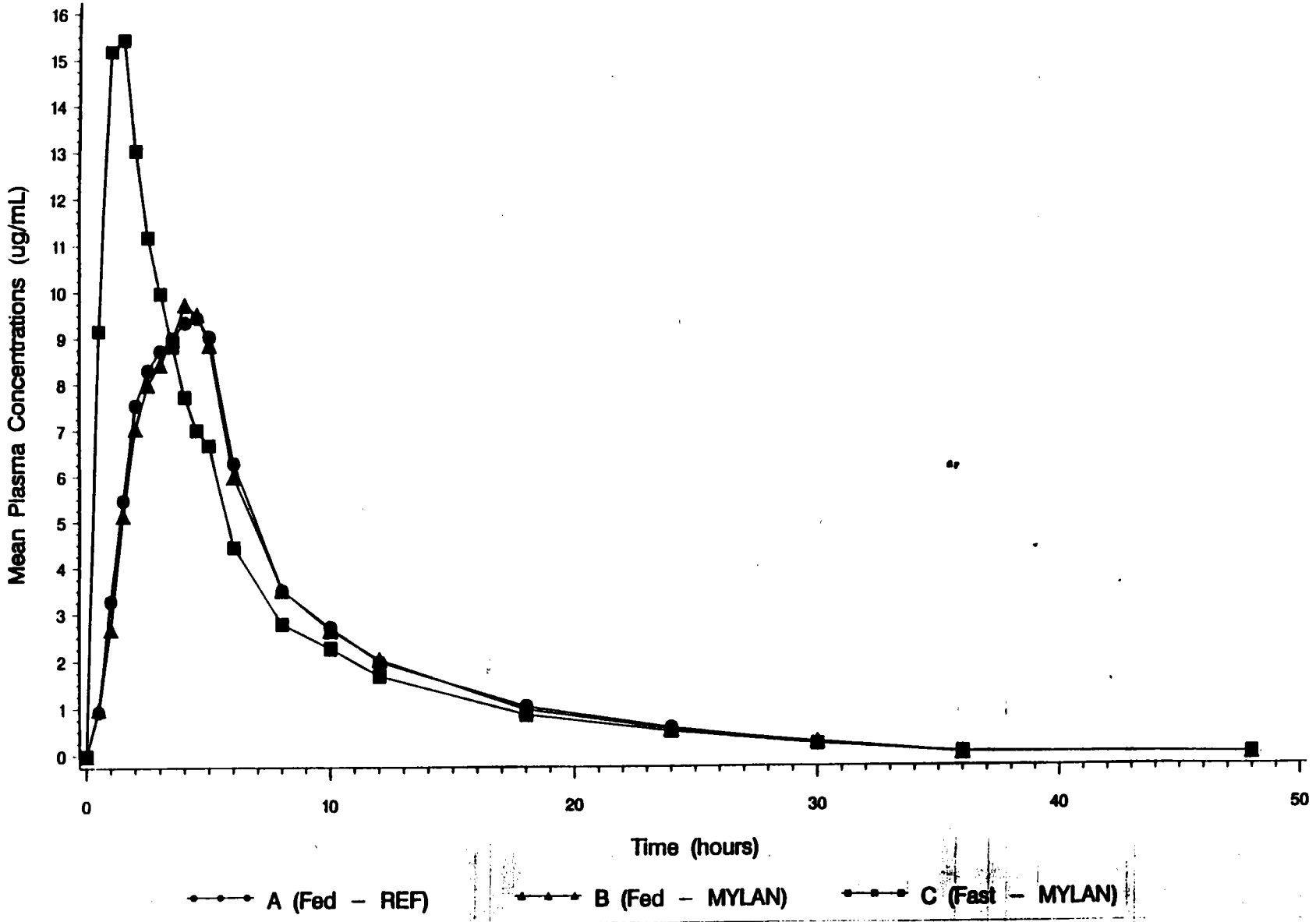
28802

ATTACHMENT 1

ETODOLAC (ETDL – 9591)

Total Dose: 300 mg (1x300mg Capsule), Study Type: Fed

Mean total Plasma Concentrations



ATTACHMENT 1